Circulation: Heart Failure

ORIGINAL RESEARCH

Defining Shock and Preshock for Mortality Risk Stratification in Cardiac Intensive Care Unit Patients

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BACKGROUND: Previous studies have defined preshock as isolated hypotension or isolated hypoperfusion, whereas shock has been variably defined as hypoperfusion with or without hypotension. We aimed to evaluate the mortality risk associated with hypotension and hypoperfusion at the time of admission in a cardiac intensive care unit population.

METHODS: We analyzed Mayo Clinic cardiac intensive care unit patients admitted between 2007 and 2015. Hypotension was defined as systolic blood pressure <90 mm Hg or mean arterial pressure <60 mm Hg, and hypoperfusion as admission lactate >2 mmol/L, oliguria, or rising creatinine. Associations between hypotension and hypoperfusion with hospital mortality were estimated using multivariable logistic regression.

RESULTS: Among 10 004 patients with a median age of 69 years, 43.1% had acute coronary syndrome, and 46.1% had heart failure. Isolated hypotension was present in 16.7%, isolated hypoperfusion in 15.3%, and 8.7% had both hypotension and hypoperfusion. Stepwise increases in hospital mortality were observed with hypotension and hypoperfusion compared with neither hypotension nor hypoperfusion (3.3%; all $P<0.001$): isolated hypotension, 9.3% (adjusted odds ratio, 1.7 [95% CI, 1.4–2.2]); isolated hypoperfusion, 17.2% (adjusted odds ratio, 2.3 [95% CI, 1.9–3.0]); both hypotension and hypoperfusion, 33.8% (adjusted odds ratio, 2.8 [95% CI, 2.1–3.6]). Adjusted hospital mortality in patients with isolated hypoperfusion was higher than in patients with isolated hypotension ($P=0.02$) and not significant different from patients with both hypotension and hypoperfusion ($P=0.18$).

CONCLUSIONS: Hypotension and hypoperfusion are both associated with increased mortality in cardiac intensive care unit patients. Hospital mortality is higher with isolated hypoperfusion or concomitant hypotension and hypoperfusion (classic shock). We contend that preshock should refer to isolated hypotension without hypoperfusion, while patients with hypoperfusion can be considered to have shock, irrespective of blood pressure.

Key Words: heart failure ■ hospital mortality ■ hypotension ■ intensive care unit ■ shock

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Cardiogenic shock (CS) represents a continuum of hemodynamic instability, including isolated hypotension with preserved organ perfusion, isolated organ hypoperfusion despite preserved blood pressure, and the combination of hypotension and hypoperfusion which has defined CS (Table I in the Data Supplement).[1–6] All previously published clinical trials of CS have required the presence of hypotension for enrollment,[2,7–10] which is consistent with established guideline definitions of CS but has resulted in a short-term mortality rate exceeding 30% to 40% despite the tested interventions.[2,5,8–11] Recent consensus documents have emphasized that CS

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The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.120.007678.

For Sources of Funding and Disclosures, see page 94.

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WHAT IS NEW?

- Shock is classically defined as hypotension with hypoperfusion, but less is known about the risk of mortality when patients suffer from isolated hypotension or hypoperfusion. This study demonstrates that both are associated with increased hospital mortality; the adjusted risk of hospital mortality among patients with isolated hypoperfusion is similar to that of patients with shock.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Using easily identifiable clinical markers, including blood pressure and invasive or noninvasive perfusion parameters, clinicians are quickly able to identify isolated preshock states associated with increased hospital mortality.
- Earlier identification of patients at risk of clinical decompensation may improve treatment pathways and assist in the prevention of more severe shock states, including cardiogenic shock.

Nonstandard Abbreviation and Acronyms

ACS	acute coronary syndrome
CICU	cardiac intensive care unit
CS	cardiogenic shock
HF	heart failure
SCAI	Society for Cardiovascular Angiography and Interventions

is defined by the presence of hypoperfusion and does not necessarily require the presence of hypotension or tachycardia.[1–3]

Less-severe hemodynamic states characterized by isolated hypotension or hypoperfusion may progress to classic CS and have been variably defined as compensated CS, impending CS, or preshock.[1,5,12] Diagnostic criteria for these intermediate states are undefined, producing uncertainty about whether these patients should be classified as having CS or preshock (Table I in the Data Supplement). Despite the variable terminology, patients with preshock have a higher risk of mortality than hemodynamically stable patients.[13] In patients with cardiac and noncardiac pathology, hypoperfusion consistently predicts worse clinical outcomes than hypotension.[13–15] The development of widely applicable criteria for preshock and shock is, therefore, imperative to identify patients who may progress to overt CS without prompt treatment and to better study these patients who have been under-represented in published CS trials. Moreover, criteria for elevated risk within specific hemodynamic subgroups may help refine CS definitions and risk stratification.

The recent Society for Cardiovascular Angiography and Intervention (SCAI) scientific statement classifies CS severity into 5 stages (A through E); CS is defined by the presence of hypoperfusion, which is a required criterion for SCAI CS stages C, D, and E.[1] Preshock is defined as isolated hypotension or tachycardia without hypoperfusion (stage B); any manifestation of hypoperfusion requiring intervention is classified as CS.[1,16] We recently demonstrated that the SCAI CS stages predict hospital mortality in the Mayo Clinic cardiac intensive care unit (CICU) population, and each higher stage was associated with increased hospital mortality.[16] As suggested by the SCAI consensus document, our study only required the presence of hypoperfusion to define CS (ie, SCAI CS stages C, D, and E), and hypotension was not included in the definition.[1,16] This led to a lower-than-expected observed mortality in patients with SCAI shock stage C and leaves uncertainty about whether hypotension should be included in future definitions of CS.[17]

The aim of this study was to evaluate the incremental predictive value of hypoperfusion and hypotension for hospital mortality in unselected CICU patients with and without acute coronary syndromes (ACS). We hypothesized that patients with hypoperfusion would be at increased risk of hospital mortality regardless of the presence of concomitant hypotension, justifying their classification as having CS.

METHODS

Study Population

This study was approved by the Institutional Review Board of Mayo Clinic (IRB No. 16-000722) as posing minimal risk to patients and was performed under a waiver of informed consent. The authors declare that all supporting data are available within the article and in the Data Supplement. We analyzed a database of consecutive unique adult patients aged ≥18 years admitted to the CICU at Mayo Clinic Hospital St. Mary's Campus between January 1, 2007 and December 31, 2015.[18–20] The Mayo Clinic CICU is a closed 16-bed unit serving critically ill cardiac medical patients. Postoperative cardiac surgery patients and patients receiving extracorporeal membrane oxygenation support are cared for in a separate cardiovascular surgical intensive care unit. To minimize the risk of survival and treatment biases associated with CICU readmission, only data from each patient's first CICU admission were analyzed.

Data Sources

We recorded demographic, vital sign, laboratory, clinical and outcome data, as well as procedures and therapies performed during the CICU and hospital stay, as previously described.[18–20] Data were extracted electronically from the medical record using the Multidisciplinary Epidemiology and Translational Research in Intensive Care Data Mart.[21] The admission value of all vital signs, clinical measurements, and laboratory values was defined as either the first value recorded after CICU admission or the value recorded closest to CICU admission. In addition,

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vital signs were recorded every 15 minutes during the first hour after CICU admission. Admission diagnoses included all *International Classification of Diseases Ninth Revision* diagnostic codes recorded on the day of CICU admission and the day before or after CICU admission; these admission diagnoses were not mutually exclusive, and the primary admission diagnosis could not be determined.

The Acute Physiology and Chronic Health Evaluation-IV predicted hospital mortality and Sequential Organ Failure Assessment score were automatically calculated for all patients using data from the first 24 hours of CICU admission using previously validated electronic algorithms.[18–20,22,23] Noncardiovascular organ failure was defined as a score ≥3 on any day 1 SOFA organ sub-score.[24] The Charlson Comorbidity Index and individual comorbidities were extracted from the medical record using an electronic algorithm.[25] Severe acute kidney injury during the CICU stay was defined as doubling of serum creatinine from baseline (the admission creatinine or most recent prior creatinine within 1 year, whichever was lower), increase in serum creatinine to ≥4.0 mg/dL or new dialysis initiation; patients with a prior history of dialysis were excluded from this analysis.[19]

Definition of Hypotension and Hypoperfusion

Hypotension was defined using systolic blood pressure and mean arterial pressure data during the first hour in the CICU (Table 1). Hypoperfusion was defined as an elevated lactate level on admission (>2 mmol/L) or acute kidney injury developing within 24 hours after admission based on a rise in creatinine level ≥0.3 mg/dL or urine output <720 mL in the first 24 hours (Table 1).[1] Patients were classified as normal (neither hypotension nor hypoperfusion), isolated hypotension, isolated hypoperfusion, and both hypotension and hypoperfusion (Table 1). The presence of tachycardia (Table 1) was considered separately, as tachycardia has not been used to define preshock in prior studies.[13]

Table 1. Study Definitions of Hypotension, Tachycardia, and Hypoperfusion

Term	Definition
Hypotension	Presence of any of the following criteria
	Admission systolic BP <90 mm Hg
	Minimum systolic BP <90 mm Hg during first 1 h
	Admission MAP <60 mm Hg
	Minimum MAP <60 mm Hg during first 1 h
Hypoperfusion	Presence of any of the following criteria
	Admission lactate >2 mmol/L
	Urine output <720 mL during first 24 h
	Creatinine increased by ≥0.3 mg/dl during first 24 h
Tachycardia	Presence of any of the following criteria
	Admission HR >100 BPM
	Maximum HR >100 BPM during first 1 h
	Admission HR>admission systolic BP
	Mean HR>mean systolic BP during first 1 h
Group	Study definition
Normal	Neither hypotension nor hypoperfusion
Isolated hypotension	Hypotension without hypoperfusion
Isolated hypoperfusion	Hypoperfusion without hypotension
Shock	Both hypotension and hypoperfusion

BP indicates blood pressure; HR, heart rate; and MAP, mean arterial pressure.

Statistical Analysis

The primary end point was all-cause hospital mortality; the key secondary end point was CICU mortality based on electronic chart review. Categorical variables are reported as number (percentage), and the Pearson χ^2 test was used to compare groups. Continuous variables are reported as median (interquartile range); the Wilcoxon rank-sum test was used to compare groups. Logistic regression was used to estimate the associations between variables of interest and hospital mortality before and after adjusting for age, sex, race, Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation-IV predicted mortality, admission diagnosis of cardiac arrest, the number of vasoactive medications, and the use of intraaortic balloon pump, dialysis, coronary angiography, percutaneous coronary intervention, and mechanical ventilation; the model was repeated after adding tachycardia as a predictor variable. Discrimination was assessed using the area under the receiver-operator characteristic curve (C statistics) value. Two-tailed *P* values <0.05 were considered statistically significant. Statistical analyses were performed using JMP Pro version 14.1.0 (SAS Institute, Cary, NC).

RESULTS

Study Population

We screened 12 904 adult admissions to the CICU during the study period and excluded 2900 patients (1877 readmissions, 755 patients without Minnesota Research Authorization, and 268 patients whose admission did not occur entirely within the study period), as demonstrated in Figure 1.[18–20] The final study population of 10 004 unique patients had a median (interquartile range) age of 669.1 (57.8–78.9) years, including 37.4% females (Table 2). The median Charlson Comorbidity Index was 2 (0–4), and the median Acute Physiology and Chronic Health Evaluation-IV predicted hospital mortality was 9.2% (3.8–21.4). Admission diagnoses (not mutually exclusive) included ACS in 43.1% patients, heart failure (HF) in 46.1% patients, and cardiac arrest in 12.1% of patients; 27.3% patients had neither ACS nor HF as an admission diagnosis. A total of 24.7% patients received vasoactive drugs during the CICU stay, including vasopressors in 20.9% and inotropes in 9.3%, and an intraaortic balloon pump was used during the CICU stay in 8.6% patients.

Prevalence of Isolated Hypotension, Isolated Hypoperfusion, and Combined Hypotension and Hypoperfusion

Hypotension present in 25.4% patients and hypoperfusion was present in 24.0% (Figure 1). Among those

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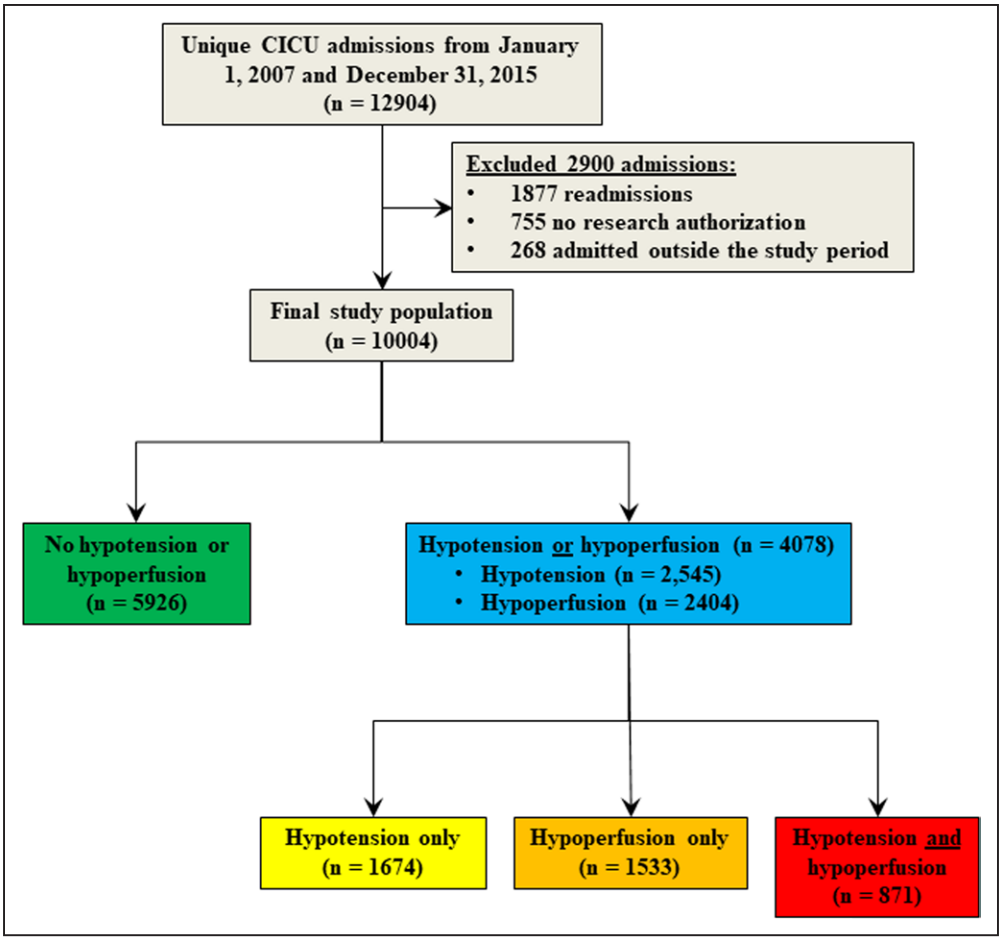
Unique CICU admissions from January 1, 2007 and December 31, 2015 (n = 12904)
Excluded 2900 admissions:
• 1877 readmissions
• 755 no research authorization
• 268 admitted outside the study period
Final study population (n = 10004)
No hypotension or hypoperfusion (n = 5926)
Hypotension or hypoperfusion (n = 4078)
• Hypotension (n = 2,545)
• Hypoperfusion (n = 2404)
Hypotension only (n = 1674)
Hypoperfusion only (n = 1533)
Hypotension and hypoperfusion (n = 871)

Figure 1. Flow diagram of inclusion and/exclusion criteria for the study population and the prevalence of isolated hypotension, isolated hypoperfusion, and both hypotension and hypoperfusion.
CICU indicates cardiac intensive care unit.

with hypotension, 26.4% had low systolic blood pressure, 26.2% had low mean arterial pressure, and 47.3% had both. The number of hypotension criteria present was one, 1028 (40.4%); 2, 865 (34.0%); 3, 370 (14.5%); and 4, 282 (11.1%). The criteria for hypoperfusion included an elevated lactate in 36.9% (41.6% of the 2135 patients with an available lactate level), low urine output in 57.7%, and rising creatinine in 32.7%. The number of hypoperfusion criteria present was one, 77.1%; 2, 18.4%; and 3, 4.5%. Among patients not initially meeting criteria for hypotension, 63.2% subsequently met one or more criteria for hypotension during the first 24 hours; this included 70.5% of patients with isolated hypoperfusion and 61.4% of normal patients. Few patients with isolated hypotension during the first 24 hours subsequently developed either an elevated lactate (6.1%) or a rise in serum creatinine meeting criteria for acute kidney injury (10.2%) during the CICU stay. A total of 2956 (29.6%) patients met criteria for tachycardia, including 2730 (27.3%) with elevated heart rate (HR) and 1319 (13.2%) with elevated shock index, including 1093 (10.9%) meeting both criteria; the prevalence of tachycardia was higher in patients with hypotension and hypoperfusion (Table 2).

Combined hypotension plus hypoperfusion was present in 8.7% patients, and 15.3% patients had isolated hypoperfusion (hypoperfusion without hypotension); isolated hypotension without hypoperfusion was present in 16.7% patients (Figure 1). Patients with isolated hypotension, isolated hypoperfusion, and both hypotension and hypoperfusion differed from patients without hypotension or hypoperfusion (Table 2). Across the normal, isolated hypotension, isolated hypoperfusion, both hypotension and hypoperfusion groups, we observed incremental increases in age, comorbidities, illness severity, laboratory abnormalities, prevalence of severe acute kidney injury and other organ failure, use of CICU procedures and therapies, and prevalence of critical care diagnoses (such as cardiac arrest).

Hospital Mortality and Isolated Hypotension, Isolated Hypoperfusion, and Combined Hypotension and Hypoperfusion

Hospital mortality increased incrementally among patients with isolated hypotension, isolated hypoperfusion, and both hypotension and hypoperfusion (Figure 2).

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Table 2. Baseline Characteristics, Comorbidities, Severity of Illness Scores, Discharge Diagnoses Admission Vital Signs, Admission Laboratory Values, Procedures, and Therapies as a Function of Hypotension and Hypoperfusion

Variable	% With available data	Normal (n=5926)	Isolated hypotension (n=1674)	Isolated hypoperfusion (n=1533)	Hypotension and hypoperfusion (n=871)	*P* value
Baseline demographics						
Age	100%	67.8 (56.6 to 78.0)	69.0 (58.6 to 78.3)	71.2 (58.6 to 80.9)	72.8 (62.2 to 81.5)	<0.001
Female sex	100%	2094 (35.3%)	684 (40.9%)	596 (38.9%)	372 (42.7%)	<0.001
White race	100%	5525 (93.2%)	1543 (92.2%)	1385 (90.4%)	783 (89.9%)	<0.001
Comorbidities						
CCI	99.8%	1 (0 to 3)	2 (0 to 4)	2 (0 to 4)	2 (1 to 4)	<0.001
Prior MI	99.8%	1132 (19.2%)	363 (21.7%)	306 (20.0%)	179 (20.6%)	0.12
Prior heart failure	99.8%	975 (16.5%)	409 (24.5%)	313 (20.5%)	256 (29.4%)	<0.001
Prior stroke	99.8%	675 (11.4%)	220 (13.2%)	218 (14.3%)	116 (13.3%)	0.008
Prior diabetes	99.8%	1585 (26.8%)	488 (29.2%)	479 (31.4%)	285 (32.8%)	<0.001
Prior lung disease	99.8%	1043 (17.6%)	381 (22.8%)	312 (20.4%)	208 (23.9%)	<0.001
Prior cancer	99.8%	1152 (19.5%)	391 (23.4%)	368 (24.1%)	224 (25.8%)	<0.001
Prior CKD	99.8%	985 (16.7%)	389 (23.3%)	402 (26.3%)	255 (29.3%)	<0.001
Prior dialysis	100%	170 (2.9%)	91 (5.4%)	174 (11.4%)	136 (15.6%)	<0.001
Admission diagnoses						
Cardiac arrest	99.0%	464 (7.9%)	177 (10.7%)	307 (20.3%)	245 (28.4%)	<0.001
VT/VF	99.0%	926 (15.8%)	255 (15.4%)	274 (18.1%)	153 (17.7%)	0.07
AF/SVT	99.0%	1697 (29.0%)	618 (37.2%)	536 (35.4%)	369 (42.7%)	<0.001
Heart failure	99.0%	2342 (40.0%)	895 (54.0%)	781 (51.6%)	545 (63.1%)	<0.001
ACS	99.0%	2643 (45.1%)	640 (38.6%)	653 (43.1%)	331 (38.3%)	<0.001
Neither ACS nor HF	99.0%	1709 (29.2%)	404 (24.4%)	402 (26.6%)	189 (21.9%)	<0.001
Sepsis	99.0%	180 (3.1%)	127 (7.7%)	134 (8.8%)	164 (19.0%)	<0.001
Respiratory failure	99.0%	798 (13.6%)	368 (22.2%)	480 (31.7%)	433 (50.1%)	<0.001
Severity of illness						
APACHE-IV mortality	100%	6.4 (2.8 to 13.4)	11.2 (5.6 to 22.7)	17.2 (7.2 to 38.5)	34.5 (17.0 to 63.9)	<0.001
Day 1 SOFA score	100%	2 (1 to 3)	3 (2 to 5)	4 (2 to 7)	7 (5 to 11)	<0.001
Noncardiovascular organ failure	100%	932 (15.7%)	575 (34.4%)	857 (55.9%)	684 (78.5%)	<0.001
Severe AKI in CICU	89.2%	356 (6.5%)	234 (16.0%)	297 (22.8%)	245 (35.2%)	<0.001
SIRS @ admission	100%	1492 (25.2%)	541 (32.3%)	711 (46.4%)	513 (58.9%)	<0.001
Tachycardia	100%	1324 (22.3%)	644 (38.5%)	498 (32.5%)	490 (56.3%)	<0.001
Therapies and procedures						
Invasive ventilator	100%	482 (8.1%)	305 (18.2%)	411 (26.8%)	409 (47.0%)	<0.001
Noninvasive ventilator	100%	755 (12.7%)	260 (15.5%)	284 (18.5%)	190 (21.8%)	<0.001
Vasoactive drugs	100%	863 (14.6%)	637 (38.0%)	5443 (28.9%)	525 (60.3%)	<0.001
Use of >1 vasoactive drug	100%	326 (5.5%)	278 (16.6%)	233 (15.2%)	345 (39.6%)	<0.001
Peak Vasoactive-Inotropic Score	99.1%	0 (0 to 0)	0 (0 to 5)	0 (0 to 3)	6.0 (0 to 33.7)	<0.001
Vasopressors	100%	647 (10.9%)	543 (32.4%)	398 (26.0%)	502 (57.6%)	<0.001
Inotropes	100%	397 (6.7%)	229 (13.7%)	147 (9.6%)	155 (17.8%)	<0.001
New vasoactive drug use between 1 and 24 h	100/%	550 (9.3%)	338 (20.2%)	220 (14.4%)	218 (25.0%)	<0.001
IABP	100%	403 (6.8%)	193 (11.5%)	139 (9.1%)	130 (14.9%)	<0.001
PAC	100%	314 (5.3%)	170 (10.2%)	119 (7.8%)	118 (13.6%)	<0.001
Dialysis	100%	158 (2.7%)	99 (5.9%)	98 (6.4%)	132 (15.2%)	<0.001
Coronary angiogram	100%	3348 (56.5%)	817 (48.8%)	754 (49.2%)	365 (41.9%)	<0.001
PCI	100%	2229 (37.6%)	537 (32.1%)	455 (29.7%)	206 (23.6%)	<0.001
RBC transfusion	100%	429 (7.2%)	282 (16.8%)	234 (15.3%)	228 (26.2%)	<0.001
In hospital CPR	99.4%	96 (1.6%)	54 (3.2%)	74 (4.8%)	89 (10.2%)	<0.001

(*Continued*)

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Table 2. Continued

Variable	% With available data	Normal (n=5926)	Isolated hypotension (n=1674)	Isolated hypoperfusion (n=1533)	Hypotension and hypoperfusion (n=871)	*P* value
Admission vital signs						
Systolic BP	99.4%	127 (113 to 144)	100 (87 to 117)	125 (110 to 144)	96 (84 to 115)	<0.001
Diastolic BP	96.2%	72 (63 to 81)	58 (48 to 69)	70 (61 to 82)	56 (46 to 68)	<0.001
Mean BP	96.2%	86 (77 to 96)	69 (60 to 80)	84 (75 to 96)	68 (58 to 81)	<0.001
Heart rate	99.4%	77 (66 to 91)	79 (67 to 95)	82 (69 to 99)	88 (70 to 107)	<0.001
Shock index	99.4%	0.6 (0.5 to 0.7)	0.8 (0.6 to 1.0)	0.7 (0.5 to 0.8)	0.9 (0.7 to 1.1)	<0.001
Respiratory rate	95.9%	18 (14–21)	18 (15–21)	18 (15–22)	20 (16–24)	<0.001
Oxygen saturation	99.4%	97 (95 to 99)	97 (94 to 99)	97 (94 to 99)	95 (92 to 98)	<0.001
Glasgow Coma Scale	97.3%	15 (15 to 15)	15 (15 to 15)	15 (14 to 15)	15 (7 to 15)	<0.001
First 24-hour urine output, L	97.0%	1.9 (1.3 to 2.8)	1.8 (1.2 to 2.8)	0.7 (0.4 to 1.5)	0.6 (0.3 to 1.3)	<0.001
Hourly urine output during first CICU day, mL/kg per h	96.6%	1.1 (0.7 to 1.6)	1.0 (0.7 to 1.6)	0.4 (0.2 to 0.9)	0.4 (0.2 to 0.8)	<0.001
Admission laboratory values						
BUN	96.0%	18 (14 to 27)	23 (16 to 37)	23 (17 to 36)	29 (20 to 46)	<0.001
Creatinine	96.3%	1.0 (0.8 to 1.3)	1.1 (0.8 to 1.6)	1.2 (0.9 to 1.8)	1.4 (1.0 to 2.4)	<0.001
Bicarbonate	96.9%	24 (22 to 27)	24 (21 to 26)	23 (20 to 26)	22 (18 to 25)	<0.001
Anion gap	89.3%	11 (9 to 13)	11 (9 to 13)	13 (10 to 15)	13 (11 to 17)	<0.001
Lactate	21.3%	1.2 (1 to 1.6)	1.2 (0.9 to 1.5)	2.7 (1.9 to 4)	2.9 (2 to 5.4)	<0.001
Arterial pH	32.3%	7.40 (7.34 to 7.44)	7.36 (7.30 to 7.42)	7.35 (7.27 to 7.41)	7.32 (7.23 to 7.39)	<0.001
Arterial base deficit	34.6%	0 (–3 to 3)	1 (–2 to 4)	3 (0 to 7)	5 (1 to 9)	<0.001
Hemoglobin	96.4%	12.5 (11.0 to 13.9)	11.6 (10.1 to 13.0)	12.0 (10.4 to 13.7)	11.2 (9.7 to 12.8)	<0.001
ALT	46.5%	29 (19 to 49)	30 (20 to 56)	40 (22 to 90)	48 (24 to 127)	<0.001
AST	46.8%	40 (26 to 79)	41 (27 to 95)	60 (31 to 180)	77 (38 to 230)	<0.001
WBC count	94.1%	9.2 (7.2 to 11.8)	9.4 (7.1 to 12.4)	10.7 (8 to 14.7)	11.6 (8.2 to 16.9)	<0.001
Outcomes						
CICU mortality	100%	84 (1.4%)	91 (5.4%)	183 (11.9%)	212 (24.3%)	<0.001
Hospital mortality	100%	196 (3.3%)	155 (9.3%)	263 (17.2%)	294 (33.8%)	<0.001
CICU LOS	100%	1.6 (0.9 to 2.6)	1.8 (0.9 to 3.1)	2.0 (1.0 to 3.6)	2.0 (0.8 to 4.0)	<0.001
Hospital LOS	100%	4.0 (2.6 to 7.5)	5.4 (2.9 to 10.5)	5.6 (2.8 to 10.4)	6.5 (2.6 to 12.0)	<0.001
ICU readmission	100%	144 (2.5%)	66 (4.2%)	64 (4.7%)	47 (7.1%)	<0.001
30-day readmission	100%	635 (11.1%)	166 (10.9%)	154 (12.1%)	80 (13.9%)	0.17

Data displayed as n (%) for categorical variables and mean±SD for continuous variables. *P* value is for χ^2 test (categorical variables) and Wilcoxon rank-sum test (continuous variables). ACS indicates acute coronary syndrome; AF, atrial fibrillation; AKI, acute kidney injury; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; CICU, cardiac intensive care unit; CKD, chronic kidney disease; PR, cardiopulmonary resuscitation; HF, heart failure; IABP, intraaortic balloon pump; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; RBC, red blood cell; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; and WBC, white blood cell.

Similar findings were observed in patients with ACS or HF (Figure 3). Hospital mortality was greater in patients with tachycardia in each of these groups (all $P<0.05$; Figure I in the Data Supplement). Patients who had isolated hypoperfusion and did not initially meet criteria for hypotension who subsequently developed hypotension had higher hospital mortality (20.3% versus 9.7%, unadjusted odds ratio [OR], 2.36 [95% CI, 1.67–3.32], $P<0.001$). After multivariable adjustment, the presence of isolated hypotension (adjusted OR, 1.74 [95% CI, 1.37–2.22]), isolated hypoperfusion (adjusted OR, 2.35 [95% CI, 1.87–2.96]), and combined hypotension and hypoperfusion (adjusted OR, 2.77 [95% CI, 2.15–3.57]) remained associated with higher hospital mortality when compared with patients without hypotension or hypoperfusion (all $P<0.001$; Figure 4). As shown in Figure 4, patients with isolated hypoperfusion or combined hypotension and hypoperfusion had higher adjusted hospital mortality than patients with isolated hypotension (both $P<0.05$), but adjusted hospital mortality was not significantly different ($P=0.18$) between patients with isolated hypoperfusion and combined hypotension and hypoperfusion. The presence of tachycardia was a significant independent predictor of hospital mortality when added to the model (adjusted OR, 1.28 [95% CI, 1.08–1.53], $P=0.005$). Among patients with ACS,

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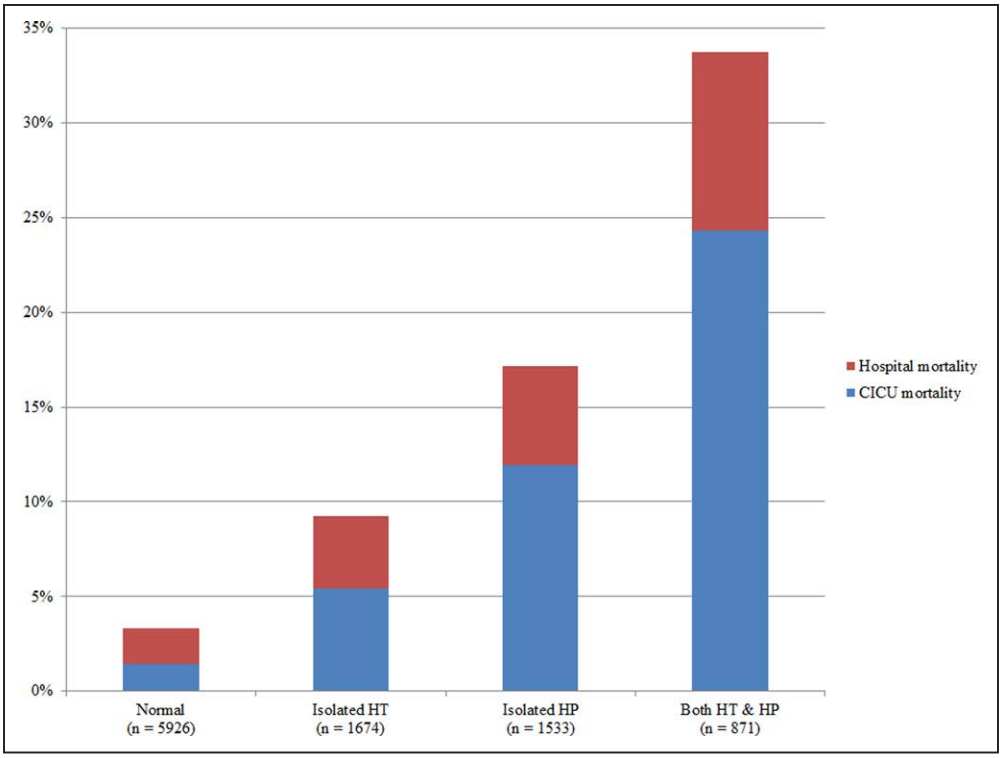

Figure 2. Cardiac intensive care unit (CICU) and hospital mortality in patients with isolated hypotension (HT), isolated hypoperfusion (HP), and both hypotension with hypoperfusion.
P<0.001 for all between groups comparisons.

those with isolated hypoperfusion had higher adjusted hospital mortality than those with isolated hypotension (*P*=0.04) and adjusted hospital mortality that was not significantly different from patients with both hypotension and hypoperfusion (*P*=0.49); among patients with HF, adjusted hospital mortality was not significantly different in patients with isolated hypoperfusion compared with either isolated hypotension (*P*=0.15) or combined hypotension and hypoperfusion (*P*=0.33).

Hospital Mortality and Number of Hypotension or Hypoperfusion Criteria

The presence of hypotension and an increasing number of hypotension criteria present were associated with progressively higher unadjusted CICU and hospital mortality (Figure IIA in the Data Supplement; *P*<0.001 for trend). Likewise, the presence of hypoperfusion and an increasing number of hypoperfusion criteria present were associated with progressively higher CICU and hospital mortality (Figure IIB in the Data Supplement; *P*<0.001 for trend). Each additional hypotension criterion (adjusted OR, 1.18 [95% CI, 1.10–1.26], *P*<0.001) and each additional hypoperfusion criterion (adjusted OR, 1.58 [95% CI, 1.41–1.78], *P* <0.001) was associated with higher adjusted hospital mortality. We observed increases in hospital mortality as the number of hypotension and hypoperfusion criteria increased (Figure 5). In addition, CICU and hospital mortality varied based on the specific criteria for hypotension and hypoperfusion which were met (Figures III and IV in the Data Supplement, respectively). Lactic acidosis was associated with higher mortality than oliguria or rising creatinine, and the 107 (1.1%) patients meeting all 3 criteria for hypoperfusion had hospital mortality exceeding 60% (Figure IV in the Data Supplement). Likewise, the number and specific type of criteria met for tachycardia (Figure VA and VB in the Data Supplement) were associated with variations in CICU and hospital mortality; patients with elevated shock index had higher mortality than patients with elevated HR.

DISCUSSION

In 10004 unselected CICU patients, the presence and severity of hypotension and hypoperfusion were associated with an increased risk of hospital mortality. CICU and hospital mortality increased incrementally among patients with isolated hypotension, isolated hypoperfusion, and combined hypotension and hypoperfusion. Mortality risk was influenced by the specific criteria met for hypotension and hypoperfusion, and the presence of tachycardia was independently associated with higher hospital mortality; all of these factors could be taken into account in future refinements of the SCAI shock stages classification. After multivariable adjustment, the presence of isolated

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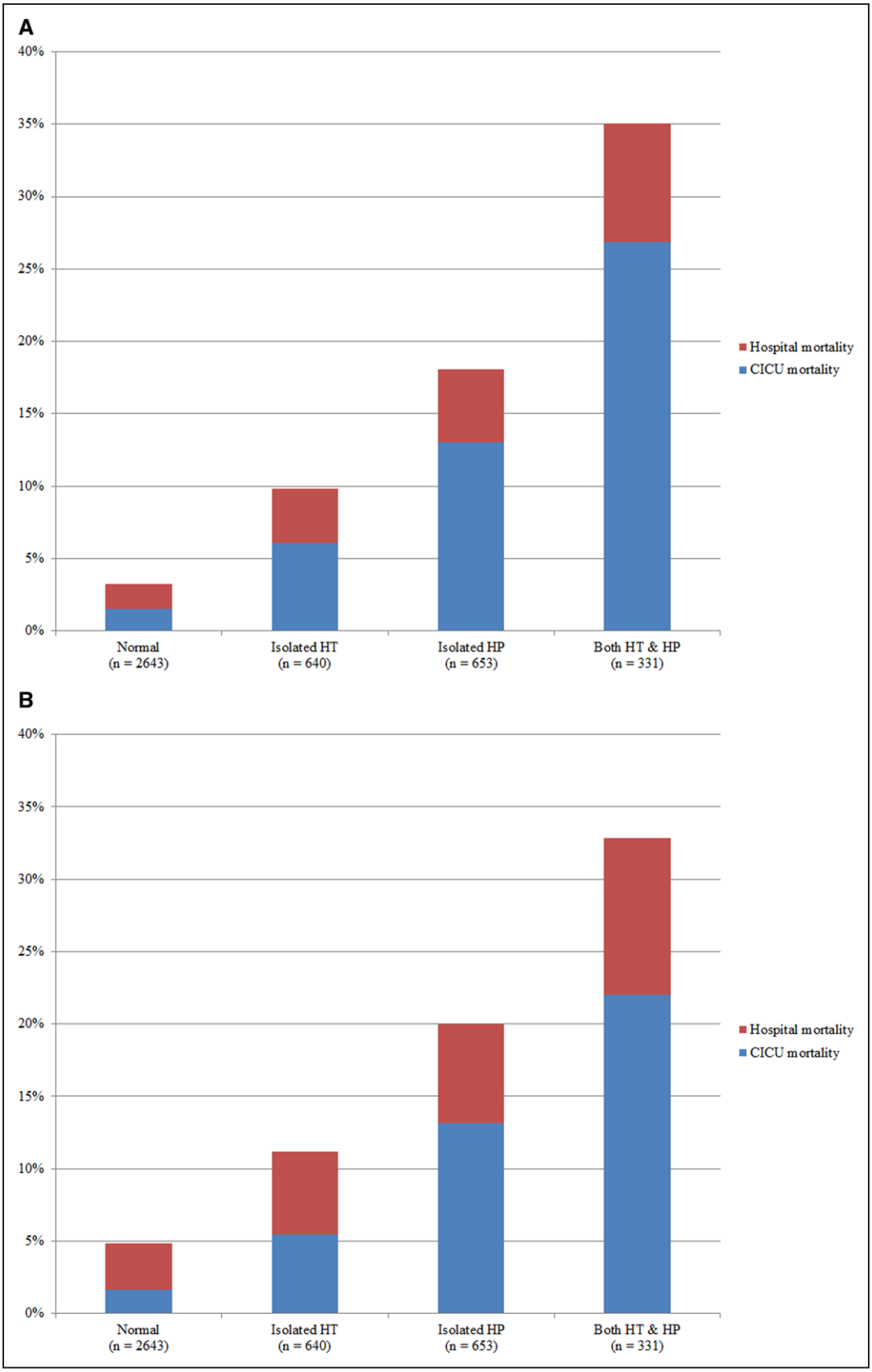

Figure 3. Cardiac intensive care unit (CICU) and hospital mortality as a function of isolated hypotension (HT), isolated hypoperfusion (HP), and both hypotension and hypoperfusion in major admission diagnosis subgroups.
A, includes patients with an admission diagnosis of acute coronary syndrome and **B**, includes patients with an admission diagnosis of heart failure. $P<0.001$ for all between groups comparisons among patients with each admission diagnosis.

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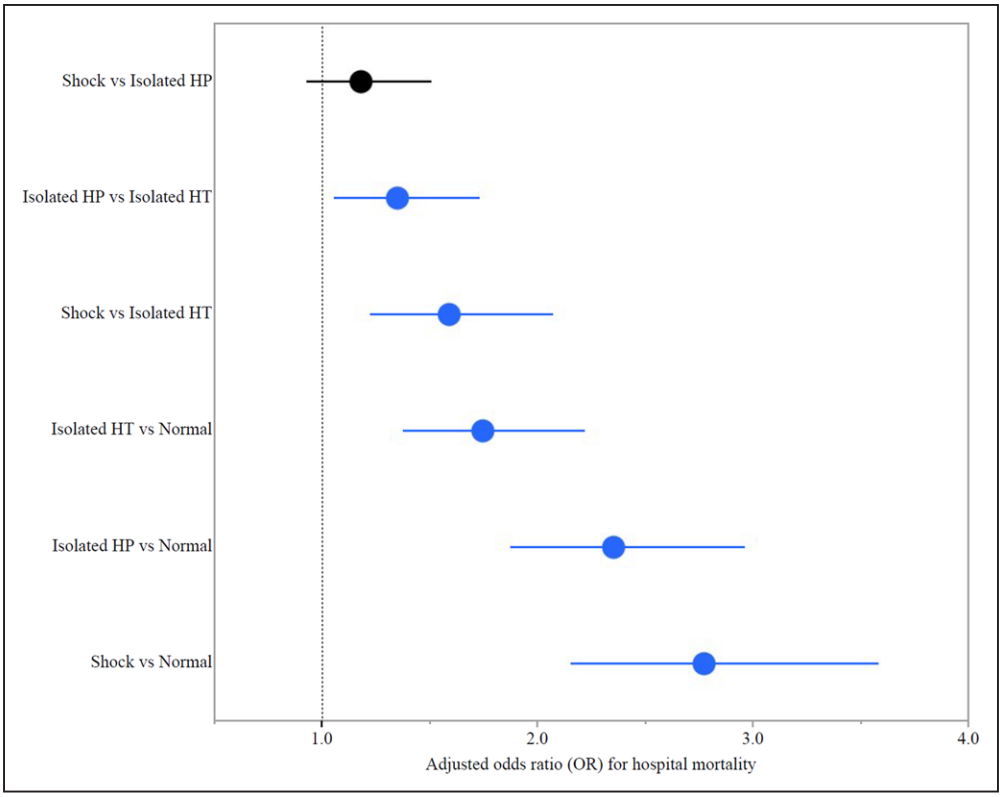

Figure 4. Forest plot demonstrating adjusted odds ratio (OR) and 95% CI values for hospital mortality for each of the hypotension (HT) and hypoperfusion (HP) groups on multivariable logistic regression.
Blue coloring represents 95% CI values that did not include 1 (ie, $P<0.05$).

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hypoperfusion was associated with a higher risk of adjusted hospital mortality compared with isolated hypotension and carried a similar risk of adjusted hospital mortality comparable to patients with both hypotension and hypoperfusion. Notably, 70% of patients initially classified as having isolated hypoperfusion developed hypotension (ie, classic CS) within the first 24 hours. These findings suggest that preshock in CICU patients should be defined as isolated hypotension, while patients with isolated hypoperfusion should be classified as having shock.

The terms preshock, compensated shock, and impending shock have been applied inconsistently to patients with various hemodynamic and physiological derangements, typically those with isolated hypotension or isolated hypoperfusion.[1,5,12,13] Patients with preshock have worse outcomes compared with patients with normal hemodynamics.[13,26] A consistent definition of preshock and shock will enable clinicians and researchers to identify these patients and to apply therapies designed to prevent clinical deterioration. Recently, Saxena et al[5] introduced the terms preshock hypotensive normoperfusion and preshock normotensive hypoperfusion to describe isolated hypotension and isolated hypoperfusion, respectively; these authors defined shock as concomitant hypotension and hypoperfusion. This study is the first to compare outcomes between these 2 proposed preshock categories, and our data demonstrate a substantially higher risk of mortality and progression to overt shock among patients with isolated hypoperfusion (preshock normotensive hypoperfusion) that warrants classifying these patients more distinctly from those with isolated hypotension (preshock hypotensive normoperfusion).[1–4,7–11]

Consistent with our findings, SCAI stage B CS encompasses preshock, defined as the presence of isolated acute hypotension without hypoperfusion.[1] Evidence from patients with ACS and HF has consistently demonstrated that hypotension on admission is associated with increased mortality.[27,28] As in our study, tachycardia and an elevated shock index have been associated with adverse outcomes in patients with ACS.[26,29] To remain consistent with prior studies, we focused on blood pressure as a primary diagnostic criterion in this study, whereas we included heart rate and shock index in the definition of SCAI shock stage B in our prior studies.[16,30]

Hypoperfusion has been defined by various clinical and biochemical parameters, including cold extremities, reduced urine output, altered mental status, and elevated serum lactate.[1] Hypoperfusion is an independent risk factor for mortality among critically ill patients with cardiac and noncardiac pathology.[14,15] In patients with CS in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial, clinical markers of hypoperfusion were the strongest predictors of 30-day mortality.[27] Patients who developed CS while

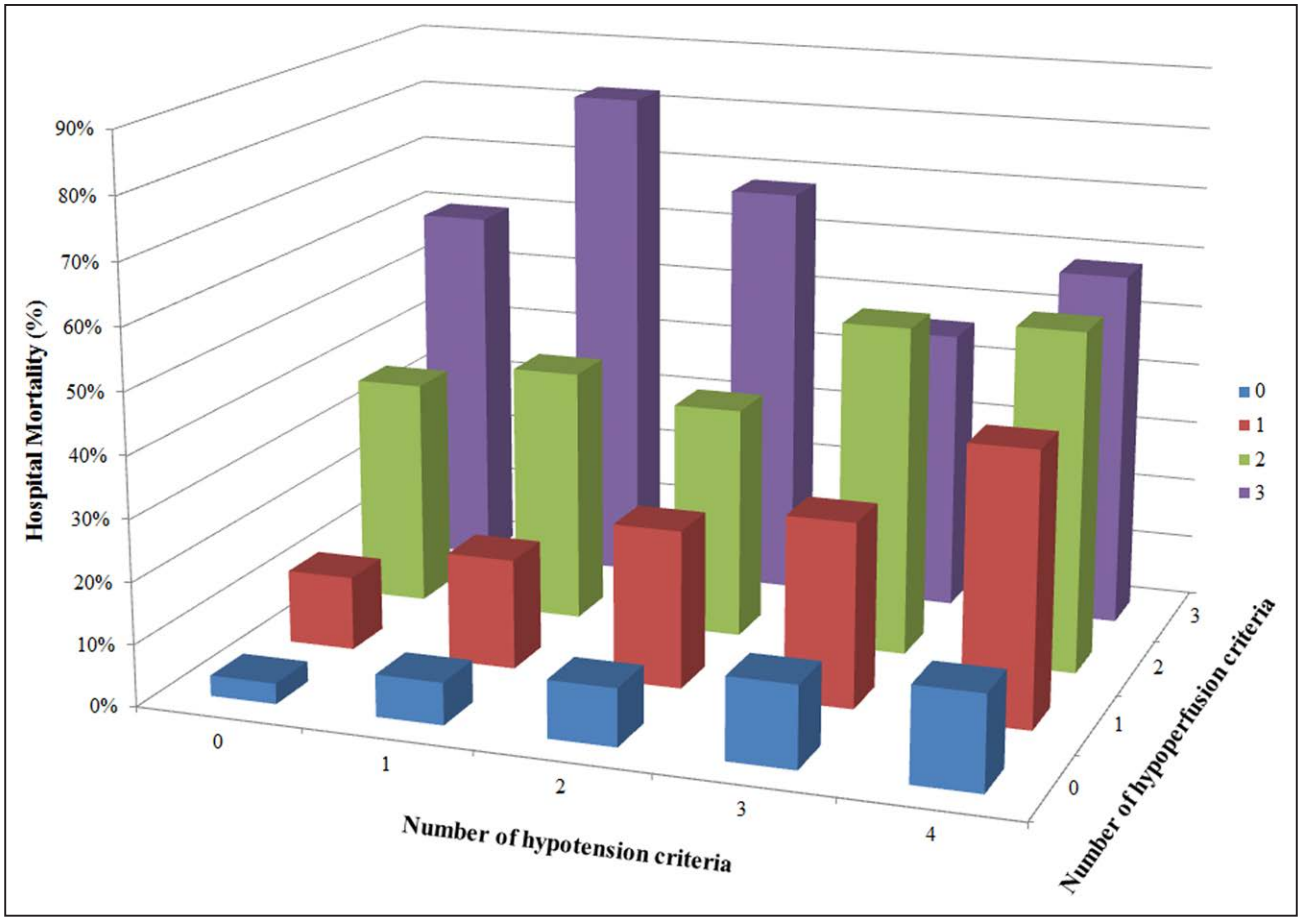

Figure 5. Hospital mortality as a function of the number of criteria for hypotension (*x* axis) and hypoperfusion (*y* axis) met by each patient.

Darker colors represent higher hospital mortality (lower survival). Both $P<0.001$ for trends across increasing number of hypotension or hypoperfusion criteria.

in hospital had increased 30-day mortality compared with patients who presented with CS on admission, which emphasizes the importance of early identification of hypoperfusion to facilitate restoration of perfusion. Identification of hypoperfusion, especially an elevated lactate level, is a critical prognostic marker in patients admitted to the CICU regardless of initial blood pressure.[2,31,32] Identification of patients in earlier shock states may, therefore, allow more favorable responses to therapies compared with those with more advanced CS and multi-organ failure.[2]

Our data recapitulate the prior analysis of the SHOCK trial registry by Menon et al[13] which demonstrated that hospital mortality progressively increased among patients with isolated hypotension, isolated hypoperfusion, and concomitant hypotension and hypoperfusion (classic CS). Patients with isolated hypoperfusion had similar filling pressures and cardiac output as those with classic CS but higher systemic vascular resistance, suggesting that a greater intrinsic compensatory response allowed these patients to maintain adequate blood pressure despite reduced cardiac output.[13] As in our study, these patients often deteriorated to classic CS, which reflects the transient nature of compensatory responses and emphasizes that CS exists on a spectrum preceded by isolated hypotension and isolated hypoperfusion.

The SCAI CS classification was developed to standardize the language describing CS to improve diagnosis, treatment, and research.[1] The SCAI paradigm emphasizes hypoperfusion as the defining characteristic of CS (SCAI stage C), while isolated acute hypotension or tachycardia without hypoperfusion defines SCAI stage B CS and can be termed preshock. Notably, the groups examined in this study differ from our prior study insofar as tachycardia was used as a criterion for defining SCAI stage B, and hypotension was not included in the definitions of SCAI stages C, D, and E in our prior study. The current study builds on our previous findings by demonstrating the incremental, independent prognostic value of hypotension and hypoperfusion and establishing the gradient in mortality that exists between preshock (SCAI shock stage B) and shock (SCAI stages C, D, and E). In addition, these new data can inform definitions of hypotension, hypoperfusion, and tachycardia for use in the clinical application of the SCAI shock stages for risk stratification.

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This study does not necessarily imply that isolated hypoperfusion (sometimes termed normotensive CS) is as dangerous as classic CS, although our results emphasize that hypoperfusion is a defining feature of shock, and we contend that patients with hypoperfusion should be classified as having shock, even in the absence of overt hypotension.[2,13] In that context, using the term preshock for nonhypotensive patients with hypoperfusion downplays their elevated risk of adverse outcomes. We, therefore, suggest that the term preshock instead be applied to patients with isolated acute hypotension without hypoperfusion, consistent with the current definition of SCAI stage B shock.[1]

Limitations

This retrospective cohort study has numerous inherent limitations, including the potential for unmeasured confounders and missing data to have influenced the results, making our findings hypothesis-generating and precluding causal inference. Indeed, given the numerous significant differences between the groups in clinically relevant variables, the observed differences in outcomes between groups could potentially be driven by residual confounding. The inclusion of a mixed CICU population without invasive hemodynamic data implies that some patients had noncardiogenic or mixed shock states. We defined hypotension and hypoperfusion using variables available within 1 to 24 hours of CICU admission, recognizing that a substantial number of patients develop CS after hospital admission; without serial vital sign and laboratory data, we cannot comment regarding the prevalence and prognostic relevance of changes between various hemodynamic states or clinical trajectories.[33] We did not have baseline blood pressure data available, so some patients with chronically low blood pressure could have been misclassified as having hypotension; this is of particular concern among patients with advanced HF who likely accounted for a substantial number of included patients. We were unable to include physical examination findings such as cool/clammy extremities or altered mental status in our definition of hypoperfusion, and we defined both hypotension and hypoperfusion without regard to the use of vasoactive drugs which could modify the relationship between these parameters and outcomes.[27] As our study population is limited to patients admitted to the CICU, our analysis cannot provide estimates of the prevalence or outcomes of shock or preshock for patients in other clinical settings, including other critical care units and non-ICU environments. Our conservative assumption that missing data were normal has limitations when compared with the use of multiple imputation techniques; this is especially relevant for potential markers of hypoperfusion such as lactate or transaminases with >50% missing data that is not likely to be missing at random.[32,34] We did perform single imputation for missing lactate levels, which reclassified 162 patients from normal to isolated hypoperfusion and 52 patients from isolated hypotension to both hypotension and hypoperfusion (as described in Materials in the Data Supplement); adjusted hospital mortality results were not materially changed from our primary analysis. We grouped patients based on the presence of ACS without distinguishing between ACS subtypes, limiting our ability to draw conclusions about CS caused by ACS.

Conclusions

Patients in the CICU can be rapidly risk stratified by routine clinical and hemodynamic parameters reflecting the presence of hypotension and hypoperfusion, both of which are associated with higher hospital mortality. Patients with isolated hypoperfusion are at increased risk of mortality compared with those with hypotension and normal perfusion, suggesting that CS exists on a spectrum defined by end-organ perfusion. Although the terminology for such patients remains controversial, based on our results we contend that the term preshock can be used to describe patients with acute hypotension but preserved organ perfusion, while patients with hypoperfusion can potentially be classified as having shock, even in the absence of acute hypotension. Identification of hypoperfusion in normotensive patients carries important prognostic relevance and should be incorporated into clinical decision making. A more structured definition of preshock will facilitate future research to determine the mechanisms by which preshock progresses to shock, and how this may be prevented. Further prospective study of patients with isolated hypotension or isolated hypoperfusion in broader populations with acute cardiovascular illness is needed to better understand their outcomes and clinical trajectories including the rate of progression to overt shock.

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Received July 15, 2020; accepted October 14, 2020.

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Sources of Funding

None.

Disclosures

Dr Baran has prior consulting relationships with Abiomed, Abbott, Getinge and Livanova and has been a speaker for Novartis.

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Supplemental Material

Supplemental Methods
Table I
Figures I–V

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